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Risk factors for loss of residual renal function in children treated with chronic peritoneal dialysis

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In dialyzed patients, preservation of residual renal function is associated with better survival, lower morbidity, and greater quality of life. To analyze the evolution of residual diuresis over time, we prospectively monitored urine output in 401 pediatric patients in the global IPPN registry who commenced peritoneal dialysis (PD) with significant residual renal function. Associations of patient characteristics and time-variant covariates with daily urine output and the risk of developing oligoanuria (under 100 ml/m^2/day) were analyzed by mixed linear modeling and Cox regression analysis including time-varying covariates. With an average loss of daily urine volume of 130 ml/m^2 per year, median time to oligoanuria was 48 months. Residual diuresis significantly subsided more rapidly in children with glomerulopathies, lower diuresis at start of PD, high ultrafiltration volume, and icodextrin use. Administration of diuretics significantly reduced oligoanuria risk, whereas the prescription of renin–angiotensin system antagonists significantly increased the risk oligoanuria. Urine output on PD was significantly associated in a negative manner with glomerulopathies (−584 ml/m^2) and marginally with the use of icodextrin (−179 ml/m^2) but positively associated with the use of biocompatible PD fluid (+111 ml/m^2). Children in both Asia and North America had consistently lower urine output compared with those in Europe perhaps due to regional variances in therapy. Thus, in children undergoing PD, residual renal function depends strongly on the cause of underlying kidney disease and may be modifiable by diuretic therapy, peritoneal ultrafiltration, and choice of PD fluid.

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Chronic dialysis is associated with high patient morbidity and mortality. Outcome studies suggest that residual renal function (RRF) is a more important determinant of patient survival, morbidity, and quality of life than the prescribed or achieved dialysis dose.[1–3] As RRF is generally considered a largely unmodifiable and rapidly diminishing fraction of fluid and solute clearance in dialyzed patients, a limited body of research has explored its determinants and amenability to therapeutic intervention. These studies have suggested a major impact of the underlying renal disease,[4–8] baseline RRF[5,9], and dialysis modality,[9–12] with possible additional effects of ethnicity,[4] gender,[4,13] obesity,[13–15] medications,[4,14,16,17] infections,[13,18] cardiovascular events,[19] and dialysis biocompatibility.[20]

RRF appears to be particularly important in dialyzed children, where it has been associated with better nutritional status and growth, cardiovascular function, and survival.[21–24]

Congenital anomalies of kidney and urinary tract (CAKUT) are the leading cause of end-stage renal disease (ESRD) in children, and these disorders are typically characterized by the preservation of high urine output even in CKD stage V. In addition, peritoneal dialysis (PD), which tends to preserve RRF better than hemodialysis,[4,9,25–27] is the dialysis modality of first choice in children.

Although the pediatric chronic peritoneal dialysis (CPD) population might be particularly well suited to study underlying conditions and therapeutic measures influencing RRF, the low incidence of pediatric ESRD has so far precluded large prospective studies assessing the course of RRF in children commencing chronic dialysis. To overcome this challenge, we interrogated the global IPPN Registry, a comprehensive prospective database encompassing more than 2000 pediatric patients undergoing CPD in 40 countries around the globe.[28] We identified 401 children who commenced CPD with significant RRF and analyzed the factors associated with the evolution of residual diuresis over time.

RESULTS

Cohort selection and patient characteristics

The selection of the study cohort from the IPPN registry population is described in Figure 1. Between April 2007 and June 2013, 2134 pediatric CPD patients were enrolled at 100 pediatric dialysis centers in 39 countries. Among 1829 patients with valid information on daily urine volume, 757 patients were incident with diuresis information reported within 3 months of CPD initiation. Of these, 161 patients were excluded because of oligoanuria (defined by daily urine output ≤ 100 ml/m^2 body surface area) at the start of CPD. Of the remaining 596 patients, 185 children with only a single urine volume measurement and 10 patients in whom urine output decreased transiently were excluded, leaving 401 children for analysis. The cohort was largely representative of the total IPPN cohort and the pediatric PD population, as reported to population-based registries in Europe and the United States (Supplementary Table S-1 online).

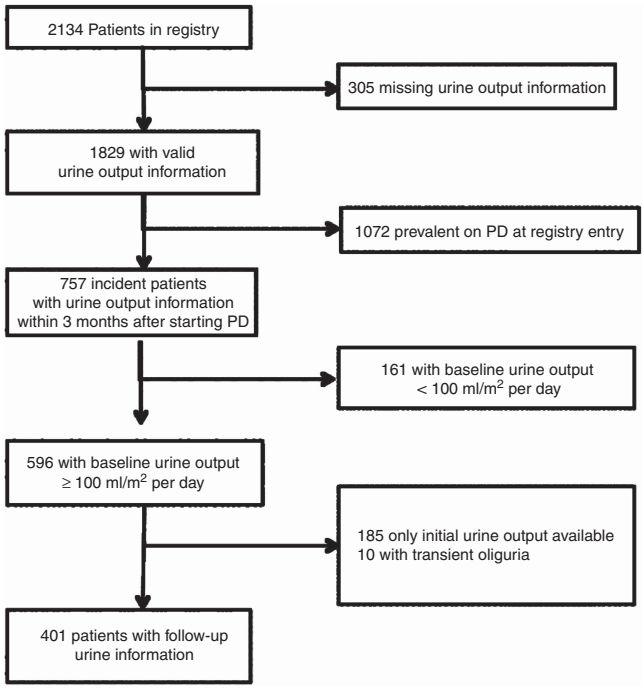

Figure 1 | Selection of study subjects. PD, peritoneal dialysis.

The characteristics of the study cohort are given in Table 1 and Supplementary Table S-2 online. The median duration of follow-up was 17 (IQR: 10–27) months. Among the 401 patients, 299 exhibited preserved diuresis during follow-up, whereas 102 developed oligoanuria. The most common primary renal diagnosis was CAKUT (50%), followed by glomerulopathies (30%). Children with CAKUT had higher urine output at PD start than patients with glomerulopathies (1.26 ± 0.71 vs. 0.77 ± 0.52 l/m^2/day), whereas eGFR tended to be lower in CAKUT patients (9.0 ± 4.5 vs.10.2 ± 5.5 ml/min/1.73 m^2).

In 180 of the 401 patients, the results of 603 twenty-four-hour urine and dialysate collections were available for analysis. Information on the peritoneal transport status obtained from Peritoneal Equilibration Tests was available in 200 subjects.

Determinants of residual diuresis

The univariate exploration of factors potentially associated with progressive loss of residual diuresis is given in Table 1. Relative to the children who became oligoanuric during the observation period, children who retained diuresis frequently had CAKUT as underlying renal disease, exhibited a larger urine output at the time of PD initiation, were exposed to lower dialysate glucose and less frequently to icodextrin, and achieved lower daily ultrafiltration rates (Table 1). They showed a lower degree of estimated fluid excess, lower blood pressure, and were administered less antihypertensive agents including renin–angiotensin system (RAS) antagonists. In contrast, patients with stable versus vanishing diuresis did not differ by age, ethnicity, body mass index, PD treatment modality, total PD fluid turnover, dialytic clearance, the use of biocompatible PD fluid or of diuretics, peritonitis frequency, and the cumulative exposure to nephrotoxic drugs (aminoglycosides and glycopeptides). The duration of follow-up was longer in patients who became oligoanuric than in those with stable diuresis (20.8 (IQR: 12.8–31.8) vs. 15.4 (8.8–25.5) months, $P = 0.001$).

Cox regression analysis was performed to identify independent risk factors of progression to oligoanuria, including time-variant covariates (Table 2). This analysis confirmed an almost fourfold higher risk of oligoanuria in patients with glomerulopathic disorders relative to those with CAKUT ($P < 0.0001$). The corresponding Kaplan–Meier survival analysis of residual diuresis revealed significantly earlier loss of urine volume in patients with glomerulopathies

Table 1 | Patient characteristics, stratified according to prospective evolution of diuresis

	All	Preserved diuresis	Oligoanuria during follow-up	*P*-value
N	401	299	102	
Total observation time (years)	1.26 (1.46)	1.10 (1.42)	1.55 (1.49)	0.001
Male sex	218 (54.4%)	171 (57.2%)	47 (46.1%)	0.052
Age (years)	9.6 (10.6)	9.9 (10.6)	8.6 (10.4)	0.285
Pubertal	162 (40.4%)	126 (42.1%)	36 (35.3%)	0.224
Ethnicity				
Caucasian	246 (61.3%)	186 (62.2%)	60 (58.8%)	0.545
Other	155 (38.7%)	113 (37.8%)	42 (41.2%)	
Gross national income (1,000 Intern'l $)	23.0 ± 11.4	22.6 ± 10.8	24.2 ± 12.8	0.216
Underlying diagnosis				
CAKUT	200 (49.9%)	175 (58.5%)	25 (24.5%)	<0.001
Glomerulopathies	122 (30.4%)	67 (22.4%)	55 (53.9%)	
Other	79 (19.7%)	57 (19.1%)	22 (21.6%)	
BMI s.d. scores	−0.26 ± 1.43	−0.23 ± 1.45	−0.36 ± 1.37	0.422
Δ Height s.d. scores per year	−0.03 ± 0.96	0.01 ± 0.90	−0.16 ± 1.08	0.106
Estimated fluid excess (%)	1.34 ± 2.43	1.07 ± 2.01	2.12 ± 3.26	0.003
Blood pressure s.d. scores				
Systolic	1.02 ± 1.39	0.85 ± 1.28	1.51 ± 1.56	<0.001
Diastolic	0.92 ± 1.33	0.84 ± 1.22	1.17 ± 1.59	0.063
Medications				
≥2 Antihypertensive drugs	125 (31.2%)	76 (25.4%)	49 (48.0%)	<0.001
RAS antagonist	129 (39.2%)	82 (33.5%)	47 (56.0%)	<0.001
Diuretics	85 (25.8%)	63 (25.7%)	22 (26.2%)	0.931
Urine output (l/m^2 per day)	1.00 ± 0.63	1.11 ± 0.69	0.67 ± 0.48	<0.001
Urinary GFR (ml/min/1.73m^2)[a]	5.2 ± 5.0	5.9 ± 5.2	2.8 ± 3.2	<0.001
Weekly Kt/V urea[a]				
Urinary	1.55 ± 2.13	1.77 ± 2.31	0.84 ± 1.13	0.004
Dialytic	1.97 ± 2.28	1.89 ± 2.56	2.22 ± 0.96	0.320
Total	3.48 ± 4.02	3.63 ± 4.54	3.01 ± 1.45	0.294
PD modality				
CAPD	97 (24.2%)	71 (23.7%)	26 (25.5%)	0.375
NIPD (APD with dry day)	188 (46.9%)	146 (48.8%)	42 (41.2%)	
CCPD (APD with wet day)	116 (28.9%)	82 (27.4%)	34 (33.3%)	
PD fluids				
Biocompatible PD fluid	171 (42.6%)	125 (41.8%)	46 (45.1%)	0.562
Icodextrin	32 (8.0%)	18 (6.0%)	14 (13.7%)	0.013
Glucose exposure (g/kg per day)	3.56 ± 2.07	3.37 ± 1.99	4.11 ± 2.20	0.002
Total PD fluid turnover(l/m^2 per day)	5.53 ± 2.67	5.43 ± 2.65	5.83 ± 2.72	0.199
Ultrafiltration volume (l/m^2 per day)	0.43 ± 0.33	0.38 ± 0.29	0.59 ± 0.39	<0.001
Patients with >1 peritonitis	142 (35.4%)	101 (33.8%)	41 (40.2%)	0.242
Exposure to nephrotoxic drugs (days)	0.8 ± 4.5	1.0 ± 5.4	0.2 ± 1.5	0.428

Abbreviations: APD, automated peritoneal dialysis; BMI, body mass index; CAKUT, congenital anomalies of kidney and urinary tract; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; GFR, glomerular filtration rate; NIPD, nocturnal intermittent peritoneal dialysis; PD, peritoneal dialysis; RAS, renin–angiotensin system. Data are given as *N* (%), mean ± s.d., or median (interquartile range). *P* values denote significant differences between patients with retained diuresis and those progressing to oligoanuria.
[a]Measured in 180 patients.

($P<0.0001$, Figure 2). It was also demonstrated that a high initial residual urine volume lowers oligoanuria risk independently of the kidney disease type ($P<0.0001$), although the annual loss of daily urine output was slightly more pronounced in patients with higher initial urine output (Figure 3). Interestingly, initial urine output was not replaceable by eGFR in predicting the oligoanuria risk. In addition, the use of icodextrin ($P=0.001$) and higher achieved ultrafiltration rates ($P=0.002$) were significant risk factors of oligoanuria. After adjusting for the underlying disease type, baseline urine output, and dialytic fluid removal, treatment with diuretics was associated with an 82% oligoanuria risk reduction during the observation period ($P=0.004$). The diuresis survival curves of children with and without diuretic therapy from the start of PD are shown in Figure 4. Conversely, the use of RAS antagonists tended to increase the risk of becoming oligoanuric ($P=0.04$). Body mass index, PD modality, and the number of peritonitis episodes did not affect the oligoanuria risk. The observed associations were independent of the region of residence.

Table 2 | Extended Cox regression analysis of factors predicting risk of developing oligoanuria

	Full model			Reduced model		
	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value
Male sex	0.961	(0.616–1.498)	0.861			
Age at initiation of PD (year)	0.953	(0.899–1.011)	0.112	0.953	(0.914–0.992)	0.026
Puberty	0.918	(0.503–1.654)	0.777			
BMI s.d. scores	1.148	(0.952–1.391)	0.153	1.154	(0.965–1.386)	0.121
Estimated fluid excess (%)	1.102	(1.006–1.200)	0.030	1.080	(0.993–1.163)	0.056
Systolic blood pressure s.d. scores	0.963	(0.834–1.109)	0.606			
Underlying diagnosis (reference: CAKUT)						
Glomerulopathies	4.134	(2.339–7.527)	<.0001	4.776	(2.791–8.467)	<0.0001
Other	2.160	(1.012–4.541)	0.043	2.607	(1.272–5.238)	0.015
Initial urine output (l/m^2 per day)	0.470	(0.285–0.743)	0.002	0.441	(0.278–0.672)	<0.0001
Medications						
RAS antagonists	1.603	(0.979–2.631)	0.061	1.546	(1.018–2.346)	0.040
Diuretics	0.170	(0.041–0.475)	0.003	0.178	(0.043–0.486)	0.004
PD modality (reference: CAPD)						
NIPD	0.974	(0.422–2.406)	0.952			
CCPD	0.861	(0.407–1.990)	0.714			
PD fluids						
Biocompatible PD fluid	0.881	(0.453–1.716)	0.710			
Icodextrin	2.380	(1.327–4.196)	0.003	2.285	(1.364–3.699)	0.001
Ultrafiltration volume (l/m^2 per day)	1.811	(1.328–2.462)	<.0001	1.885	(1.253–2.120)	<0.0001
No. of peritonitis episodes	0.992	(0.790–1.205)	0.937			
Nephrotoxic drug exposure (days)	0.905	(0.751–1.067)	0.263			
Region of residence (reference: Europe)						
United States	0.928	(0.279–2.623)	0.895			
Latin America	0.563	(0.230–1.349)	0.201			
Turkey	0.905	(0.751–1.067)	0.263			
Asia	1.050	(0.473–2.280)	0.090			

Abbreviations: BMI, body mass index; CAKUT, congenital anomalies of kidney and urinary tract; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; PD, peritoneal dialysis; NIPD, nocturnal intermittent peritoneal dialysis; RAS, renin–angiotensin system.

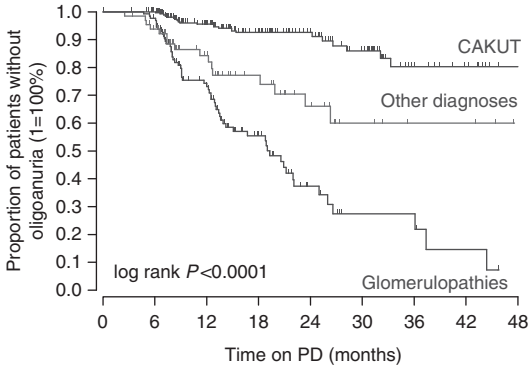

Figure 2 | Survival of residual diuresis by the renal diagnosis group.

A separate proportionate hazard analysis was performed for the subgroup of patients with available Peritoneal Equilibration Test information. The hazard ratio to turn oligoanuric did not differ between patients with low, low-average, high-average, and high transporter status (overall $P = 0.487$).

In addition to the extended Cox regression analysis of the oligoanuria risk performed on the entire cohort, we utilized mixed linear modeling to identify factors predicting residual urine volume at any time on PD as a continuous variable in those 180 patients in whom precise urine volume measurements from 24-h urine collections were available (Table 3). All factors significantly associated with the development of oligoanuria (Table 1) were offered for inclusion in the model. A strong linear trend toward lower diuresis with time on dialysis was observed ($P < 0.0001$); a mean annual loss of 138 (95% confidence interval: 92 to 184) ml/m^2 residual urine volume was calculated by univariate regression for the population as a whole (Table 3, Model 1). Independently of time on dialysis, the diagnosis of glomerulopathy or other non-CAKUT disease and the use of icodextrin were associated with lower urine output, whereas the use of biocompatible PD fluids and, at borderline significance, diuretics positively predicted residual urine volume. As some factors such as PD duration and the use of biocompatible PD fluid, icodextrin, and diuretics strongly differed by region (see Supplementary Table S-1 online), another model including the region of residence was calculated (Table 3, Model 2). This analysis disclosed that patients in the United States, Turkey, and Asia

had consistently lower urine output than children treated in Europe. The inclusion of region variably attenuated the effect of diuretics, biocompatible PD fluid, and icodextrin.

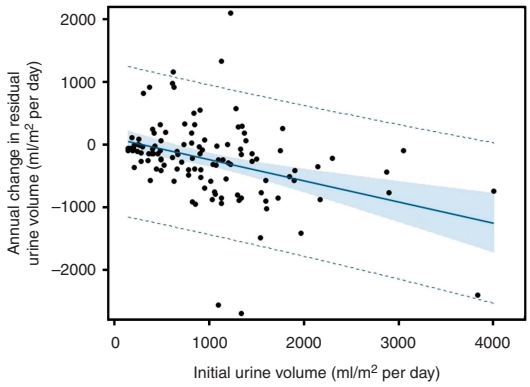

Figure 3 | Association of initial urine output and the subsequent annualized loss of residual diuresis ($R^2 = 0.1389$, $P < 0.0001$).

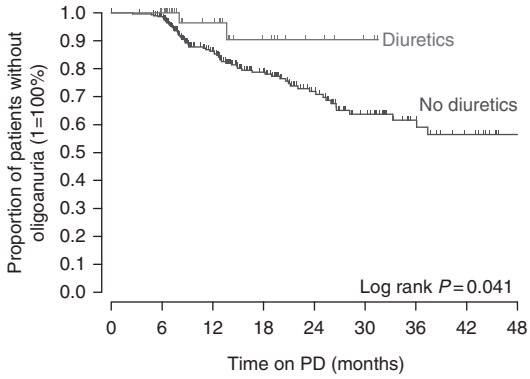

Figure 4 | Survival of residual diuresis in 45 patients receiving diuretic therapy compared with patients without diuretics.

DISCUSSION

Our prospective study in a large cohort of children commencing CPD defines key determinants of residual diuresis in the pediatric ESRD population. Among more than 750 children starting PD, 80% still had significant urine output. For these, the median time to oligoanuria while on PD was 4 years. Hence, although RRF declines with time on dialysis, a large proportion of pediatric PD patients enjoy extended preservation of urine output.

The most important cause for the relatively slow overall loss of residual diuresis was the high proportion (50%) of children with underlying CAKUT. Children with these disorders were four times less likely to develop oligoanuria and had on average >600 ml/m^2 higher daily urine output than children with ESRD due to glomerulopathies at any time during the observation period. Although we cannot completely exclude the possibility of overestimated hazard ratios due to informative censoring (e.g. renal transplantation being a competing event), our findings are in keeping with previous reports of glomerulopathies being a risk factor for rapid loss of urine output in adult populations.[4–8] Whereas in adult patients diabetic nephropathy is by far the most prevalent glomerular disease,[4,7,8] hereditary podocyte disorders are the most common type of glomerulopathy in children. Our findings indicate that these disorders are prone to rapid loss of RRF in a manner similar to what occurs with the acquired glomerular diseases causing ESRD in adults.

We confirmed previous reports that high urine volume at initiation of PD is predictive of sustained diuresis.[9] It is noteworthy that this effect was independent of the underlying kidney disease type, suggesting that CAKUT patients maintain diuresis on dialysis intrinsically better than children with other kidney disorders. The effect of disease type was also independent of blood pressure, which, as expected, was higher in the glomerulopathic patients.

Table 3 | Mixed linear model analysis of factors predicting residual urine volume

Variables	Model 1			Model 2		
	Estimate	s.e.	*P*-value	Estimate	s.e.	*P*-value
Intercept	1125	104	<0.0001	1350	106	<0.0001
Time on PD (years)	−138	23	<.0001	−134	23.4	<0.0001
Underlying diagnosis (ref. CAKUT)						
Glomerulopathies	−614	103	<0.0001	−584	101	<0.0001
Other	−395	145	0.007	−330	142	0.021
Use of diuretics	103	59	0.074	84	61	0.165
Use of biocompatible PD fluid	121	59	0.028	111	58	0.057
Use of icodextrin	−202	100	0.043	−179	103	0.083
Ultrafiltration volume (l/m^2 per day)	−35	23	0.138	−42	24	0.077
Region of residence (ref: Europe)						
North America				−431	215	0.047
Latin America				46	120	0.705
Turkey				−259	131	0.050
Asia				−420	153	0.007

Abbreviations: CAKUT, congenital anomalies of kidney and urinary tract; PD, peritoneal dialysis.
Daily urine output per m^2 body surface area was used as the dependent variable in the model. Estimates denote ml/m^2 diuresis difference attributable to predictor variable (per one unit for quantitative variables).

It is also of note that patients with CAKUT did not have better eGFR at the start of PD, and the lower oligoanuria risk attributable to high urine output was not replaceable by eGFR. Hence, the advantage of CAKUT patients is limited to the preservation of urine output rather than small-solute clearance.

A notable finding of this study is the positive impact of diuretics on maintaining residual urine output. Children who received diuretics from the initiation of PD were 80% less likely to become oligoanuric than untreated patients. Our findings represent the first evidence suggesting effective stimulation of residual diuresis by diuretics in dialyzed children. The findings of this observational study are in keeping with the results of a randomized controlled trial in adults on CPD in which furosemide increased urine volume without affecting creatinine and urea clearance;[29] in contrast, another adult study observed a faster decline of residual GFR associated with diuretic usage.[30] The efficacy of diuretics is also controversial in the adult hemodialysis population.[16,31] In view of the crucial role of fluid balance in preventing cardiovascular morbidity in the dialysis population, our findings should stimulate interventional studies to further evaluate the efficacy of diuretic therapy in pediatric and adult dialysis patients.

The observed associations of higher daily ultrafiltration rates and icodextrin use with lower urine volumes and a higher risk of oligoanuria may reflect the efforts for enhanced dialytic fluid removal in patients with failing RRF. However, the observational nature of our study does not allow us to exclude the alternative interpretation of a causative detrimental impact of higher ultrafiltration on residual diuresis. Of interest in this context, in a randomized controlled trial in adult PD patients, the use of icodextrin was associated with a statistically insignificant but slightly more rapid loss of RRF over time.[32] In contrast, a recent systematic review concluded that icodextrin improves peritoneal ultrafiltration without compromising RRF or urine output.[33]

Several randomized clinical trials in adult PD patients evaluated a potential effect of the use of biocompatible PD fluids with low glucose degradation product content on the preservation of RRF.[34–38] Most studies reported better preserved urine output with low glucose degradation product solutions, with a somewhat less consistent effect on small molecule clearance. A recent meta-analysis of seven randomized clinical trials encompassing 520 adult patients identified a mean difference of 126 (95% CI 27–226) ml urine volume per day in favor of biocompatible PD fluids.[20] Our multivariate analysis of 180 children attributed a marginal increase of daily urine volume (111 ± 58 ml/m^2) to the use of biocompatible PD fluids, although the risk of developing oligoanuria was not reduced.

Blood pressure is a well-established risk factor for the loss of renal function in pre-dialytic CKD both in adults and children, as well as in incident adult dialysis patients.[39,40] In this pediatric PD population, blood pressure was not predictive of residual urine volume or the risk of developing oligoanuria. Although the KDIGO clinical practice guideline recommends RAS inhibition in CKD, few previous studies addressed a potential effect of RAS antagonist therapy on RRF. In 1032 incident adult PD patients followed in a Canadian national registry, the use of ACE inhibitors was associated with a reduced risk of RRF loss defined by urine output <200 ml per day.[4] Smaller single-center studies yielded conflicting results regarding the impact of RAS blockade on RRF.[8,17] In our pediatric study, RAS blockade did not appear to preserve overall residual urine volume but marginally increased the risk of developing oligoanuria. We speculate that the pediatric PD population may be at greater risk of episodic volume depletion compared with adults, due to a higher incidence of gastrointestinal and febrile infections in childhood adding to increased urinary fluid and electrolyte losses characteristically present in patients with dysplastic kidney disease. In this setting, RAS blocker therapy might increase the risk of episodic renal hypoperfusion leading to irreversible oligoanuria.

In the same context, studies performed in the 1990s observed that frequent peritonitis episodes predisposed to a rapid loss of RRF.[18] We did not observe an association of the number of peritonitis episodes or the duration of exposure to nephrotoxic antibiotics with the evolution of residual diuresis. The markedly decreased overall incidence, earlier detection, and more efficient treatment of peritonitis accomplished in recent years may have largely eliminated the impact of PD-associated infections on RRF.

The estimated deviation of actual body weight from 'dry' weight did not predict urine volume over time and tended to be associated with an increased oligoanuria risk. This finding does not support the widespread notion that urine output increases with fluid overload.

Other risk factors for RRF loss identified previously in adult patients, i.e. male sex and obesity, were also not found to be significant in our study. This may be explained by the limited number of sexually mature individuals and the low prevalence of obesity in this global pediatric population.

A potential limitation of this study concerns the generalizability of our findings. As reporting to the IPPN Registry is voluntary, we cannot entirely exclude selection bias related to the type of centers reporting to the registry, the patients reported by a particular center, and the availability of urine output information. However, we found the study cohort to be largely representative of the entire IPPN cohort and other international pediatric RRT registry populations regarding the distribution of age and eGFR at the start of PD, as well as the underlying renal disease spectrum (Supplementary Table S-1 online). Likewise, the average follow-up time on PD was comparable to that of the total incident patient population and, at least for the European countries including Turkey, matched those recently reported by the population-based ESPN/ERA-EDTA Registry.[41]

Global data collection is both a strength and a limitation of the IPPN Registry. Although studies as the one presented here only become possible by the contribution of multiple

pediatric dialysis centers around the globe, regional differences in PD populations and treatment practices might influence observed outcomes. Global adjustment for region, as performed in this study, is generally considered appropriate, although some residual confounding cannot be ruled out. Indeed, we noted a lower prevalence of CAKUT in Asia, more frequent use of diuretics, icodextrin, and biocompatible PD fluids in Europe, and less frequent automated PD use in Turkey. The preliminary conclusion from our multivariate analyses is that residual urine output generally differs between regions, but the region of residence probably does not affect the risk of becoming oligoanuric while on PD.

In summary, in this large pediatric cohort study, we identified that, although substantial urine output is frequently maintained in children undergoing CPD, underlying glomerulopathies and dialysis prescriptions resulting in high ultrafiltration rates are risk factors for rapid progression to oligoanuria. The increased volume and/or duration of urine output associated with the use of diuretics and biocompatible PD fluids are notable observations that might deserve evaluation in controlled interventional trials.

MATERIALS AND METHODS

Data collection

The IPPN Registry collects information from infants, children, and adolescents treated with CPD around the globe. Participation in the registry is voluntary. The participating centers are asked to enroll all prevalent and incident consenting patients and follow them until discontinuation of PD.

Data input to the IPPN Registry is performed exclusively via an Internet-based web platform (www.pedpd.org). Data pertaining to basic patient and PD modality characteristics, growth and weight gain, nutritional modalities, intercurrent hospitalizations, hematology and serum biochemistry, medications, dialysis prescription, daily residual urine volume and ultrafiltration, and, optionally, echocardiography and ambulatory blood pressure monitoring results are submitted every 6 months. In addition, PD-related infections and access revisions and the findings of any Peritoneal Equilibration Tests, and renal and dialytic clearance studies are reported whenever these are performed. Data entries are automatically checked for plausibility and completeness. Data protection is ensured by de-identified data input. The registry protocol was approved by the ethical committees/institutional review boards as required at each participating center. Written parental consent and, whenever appropriate, assent from patients were obtained.

Statistics

Data are expressed by absolute and relative frequencies, mean $\pm$ s.d. for normally distributed variables, and by median and interquartile range for variables with skewed distribution.

Systolic and diastolic blood pressure was converted to s.d. scores adjusting for age, sex, and height according to the methods published in the NHBPEP Fourth Report.[42] Residual GFR was calculated as the mean of urinary creatinine and urea clearance.

Between-group differences were assessed by Pearson's χ^2-test, a *t*-test, or the Wilcoxon rank-sum test as appropriate. Extended Cox proportional hazard modeling was applied, incorporating time-variant covariates and censoring patients with retained diuresis at last observation. For the analysis of diuresis 'survival' by diuretic use patients was censored when diuretics were discontinued (treatment group) or initiated (no-treatment group). Kaplan–Meier survival analysis with log-rank significance testing was performed to illustrate the effect of key factors associated with preservation of urine output. For the assessment of urine volume over time, general mixed linear models were fitted to account for the dependent data structure within the same patient (random intercept and slope) applying a spatial (spherical) covariance structure based on the Akaike information citerion. Possible covariates were included, and results are given both for full and reduced models. The latter were constructed by backward variable selection with a selection margin of $P<0.2$. The annualized change in urine volume was calculated from the first and the last observed value and plotted against baseline urine volume within a regression plot including 95% prediction and confidence bands. Data were analyzed using SAS 9.2 (SAS Institute, Cary, NC, USA).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Distribution of age, primary renal disease and eGFR at initiation of dialysis in present cohort, all incident patients in IPPN, European children starting PD reported to ESPN/ERA-EDTA Registry, and pediatric patients reported to United States Renal Data System (USRDS).

Table S2. Patient characteristics at commencement of PD according to region of residence.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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